

## REMARKS

Claims 1-7 are pending. Claims 2, 5, 6 have been amended. Claims 8-34 have been cancelled. No new matter has been added.

### *Correcting Inventorship*

Please correct the inventorship of the application by deleting Yibing Yan, and Lisa Alaimo as inventors. The invention of Yibing Yan and Lisa Alaimo is no longer being claimed in this application. The processing fee under 37 CFR 1.17(i) is being submitted herewith.

### *Rejection of Claims 2, 5, 6, 14, 17, 18, 32 and 33 Under 35 U.S.C. §112, second paragraph*

Claims 2, 5, 6, 14, 17, 18, 32 and 33 are rejected under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention." In particular, the Examiner states that claims 2 and 14 are "vague and indefinite because it is not clear what range of percentages is being claimed."

Claim 14 has been cancelled and claim 2 has been amended to recite "at least about 60%", thereby obviating this rejection.

The Examiner also states that

Claims 5, 6, 17, 18, 32 and 33 recite "...at least one additional agent ..." [and] this is vague and indefinite because it sounds as if more than one agent can be added to the claims. While the instant specification discusses aspirin as an agent of use in certain instances of inflammation, ... it does not appear that aspirin is envisioned for use in the instant invention, nor are additional agents discussed.

Applicants have cancelled claims 17, 18, 32 and 33 and have amended the claim 5 and 6 to recite that the method further includes administering at least one agent that blocks platelet aggregation or that enhances thrombolysis. Thus, the pending claims clearly recite that the method includes administering a CD154 inhibitor and at least one agent that blocks platelet

aggregation or that enhances thrombolysis. Such methods were clearly contemplated by the application. See, e.g., page 7, lines 25-26 of the application. Therefore, the claims as amended are clear, and Applicant respectfully requests that the Examiner withdraw this rejection.

***Rejection of Claims 1-34 Under 35 U.S.C. §103(a)***

Claims 1-34 are rejected under 35 U.S.C. §103(a) as being “unpatentable over Stetler-Stevenson (USPN 5,595,885) and the Millennium product sheet in view of Shafer (USPN 6,232,315). Specifically, the Examiner states that

Stetler-Stevenson teaches that metalloproteinases play an important role in disease processes characterized by the inappropriate destruction of the extracellular matrix. The diseases include inflammatory processes ... Stetler-Stevenson does not teach a method of inhibiting thrombosis.

The Millennium product data sheet discloses INTEGRALIN (eptifibatide) works by preventing the clumping together of blood cells known as platelets. ... Millennium does not teach a method of treatment for inflammatory disease.

Shafer teaches a method for treating inflammatory disease in a patient which comprises treating a patient with a combination comprising a thrombin inhibitor and a NSAID. Shafer discloses that thrombin inhibitors, which inhibit formation of blood clots, are effective for inhibiting inflammation. ...

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the TIMP-2 of Stetler-Stevenson with the eptifibatide of Millennium in order to treat inflammatory disease and thrombosis, as Shafer has done with a combination of an anti-inflammatory agent and a thrombin inhibitor. While Stetler-Stevenson does not specifically teach that TIMP-2 inhibits the release of soluble CD154, absent some evidence to the contrary, the TIMP-2 disclosed by Stetler-Stevenson would inherently possess this property.

Applicants respectfully traverse this rejection. Claims 8-34 have been cancelled. Claims 1-7 are directed to methods of treating thrombosis by administering a CD154 inhibitor, e.g., a metalloproteinase (MMP) inhibitor, to a subject in an amount effective to inhibit the release of soluble CD154 from a platelet. In some of the dependencies, the method can further include administration of an agent that blocks platelet aggregation or that enhances thrombolysis such as the GP IIb-IIIa antagonist eptifibatide.

As admitted by the Examiner, the Stetler-Stevenson references does not teach or suggest a method of treating thrombosis using a CD154 inhibitor such as TIMP-2. In fact, the Stetler-Stevenson reference provides absolutely no suggestion that TIMP-2 acts as an inhibitor of CD154, or that TIMP-2 can inhibit platelet aggregation or thrombosis. Thus, Stetler-Stevenson does not teach or suggest the methods of claims 1-7.

The Millennium reference discusses eptifibatide, an agent which inhibits platelet aggregation. The Millennium reference does not even mention CD154 inhibitors—forget teach or suggest that a CD154 inhibitor such as TIMP-2 can be used to treat thrombosis. The Shafer et al. references discusses treating inflammation, and thus has no relevance to claims for treating thrombosis or inhibiting platelet aggregation. As such, neither the Millennium reference nor the Shafer et al. reference, make up for the deficiencies of the Stetler-Stevenson reference. Thus, none of the references cited by the Examiner, either alone or in combination, teach or suggest the invention of claims 1-7.

For the reasons discussed above, Applicants respectfully request that the Examiner withdraw this rejection.

A check for the processing fee under 37 CFR 1.17(i) is being submitted herewith. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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